

Division of Diabetes Treatment and Prevention

Impact of Diet and Lifestyle Changes from the Past on Inflammatory Processes and Disease in AI/AN Today

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Dr. John Umhau:

It's really great to be able to talk to you all about the things that I've been learning lately. I got interested in nutrition and the brain years ago, and it seems that there wasn't quite enough known about it. When I was a doctor and when I was in medical school and very interested in all these things, and it turns out that when I was working on the street, with homeless people in D.C., that a lot of the guys that I was taking care of had problems with their brain. They weren't working right.

I came to think that perhaps, their brains were part of the reasons why they were homeless. So, I got interested in what they were eating because they had terrible diets. This is sort of what drove me to work at NIH. I went to work with the Alcoholism Institute for 20 years. I admitted folks to the Detox Unit and we did all kinds of studies, but I have always been mostly interested in diet and how that might be affecting the brain and how we think. Well, once I got to Indian country a few years ago, it was obvious that the same issues that were affecting my homeless people in the way they were thinking were also affecting metabolism, and particularly, could very well be the same kind of causes that we think of when we think of the causes for diabetes.

So, this talk is really designed to give you an introduction to some of the newest and latest thinking about diet and diabetes. Although much of what I'm going to present follows clearly from the latest research, it's really new, and there are no clear answers to many questions. We just lack the definitive studies necessary to tell us all we need to know. So, please keep in mind that this lecture is intended to give you background into whatever new guidelines will be developed one day. This talk may bring up questions about what you've been taught in the past, but hopefully, will stimulate your curiosity about what is really the best dietary advice to give because right now, we just don't really know.

The main idea I want to share with you is not only about diabetes, but also, many of the other problems that our patients deal with, such as the metabolic syndrome, obesity, alcoholism, depression are related to increased inflammation that may be in response to excessive bacterial products coming from the gut. The good news, which is probably intuitive for many of us, is that many aspects of traditional Native American lifestyles reduce inflammation that causes these problems.

Bottom line is that there's a real biological reason for us to avoid what we know is not good for us. We know we need to avoid soft drinks, especially those containing high fructose corn syrup. We need to avoid omega-6 laden fatty foods. And we need to avoid lack of exercise. We need to have more outdoor exercise which will give us more sun exposure and Vitamin D.

So, this next slide is a cross-section that sort of summarizes what I want to mostly get across today. This is a cross-section of the intestines and the blood vessels that carry away nutrients and bacterial products from the gut. The main idea here is that under certain situations, humans are influenced by material from the gut bacteria which is called a "gut biome." This is really an area of research



that's on the cutting-edge. Recently, I read a research paper where one researcher theorized, that since gut bacteria can manufacture neurotransmitters, perhaps, some particular species of bacteria may be signaling the brain to cause a craving for the particular type of food that those particular species of bacteria want for their survival.

We have no idea how important this is or how important it might be for humans, but it's really fascinating to me. What we know most about however, is that the material from dead gram-negative bacteria cell walls which is called lipopolysaccharide or LPS, or I call it "endotoxin" in this talk. This material can get into the body and it causes an inflammatory reaction. There are many bacterial substances from the gut that have important effects, but there's a growing body of evidence suggesting that this endotoxin is a key driver of the inflammatory response that cannot only induce insulin resistance, but also induce inflammation throughout the body, including the brain.

As I looked into this, it was fascinating to find that so many common diseases have an inflammatory cause that can be traced to the effect of endotoxin. People have noticed that there are a number of common disorders that seem to occur together, and since they're all caused, at least to some extent by inflammation, I kind of call them "common inflammatory syndromes," or CIS. Now, these common inflammatory symptoms have many different risk factors in common. And it seems like the inflammation from endotoxin seems to be implicated in each one of these, which is kind of interesting. I'll explain more about this as we go through my talk here.

Now, these disorders have many risk factors in common, stress, smoking, sedentary lifestyle, even gingivitis. These all are related to the increased inflammatory effect of endotoxin. Normally, the gut contains a wide diversity of bacteria, the more diverse, the better. These bacteria help us digest our food and can keep us healthy. However, when there are fewer types of bacteria, this reduced diversity of the gut biome can be unhealthy, especially when there are too many of the gram-negative bacteria that produce endotoxin. Excess gram-negative bacteria can result from bacterial overgrowth. This can happen when gut motility is disturbed say from chronic opioid pain medication is administered. Also, under certain circumstances, the gut can become more permeable or leaky, allowing the excess endotoxins to end up in circulation. This can occur because of inflammation, because of stress, because of food sensitivities such as gluten and also because of the effect of certain gut microbes, and there are other reasons too.

Some level of endotoxin from the gut is normal and will reach the liver portal circulation. But in the excessive amounts, this endotoxin can cause liver and systemic inflammation. When you see someone with a beer gut or pot belly, the fat that is causing this really abnormal body appearance is from the omentum. This is the layer of the fat that surrounds the intestines. This fat is actually inflamed by excessive endotoxin leaking from the gut.

Endotoxin, as we mentioned before, can stimulate fat and other cells to become insulin resistant. And there's a lot of evidence, growing evidence, that this process is key to the development of fatty liver disease, the metabolic syndrome, and diabetes. This is what they call a survival graph, and it's from one study that I think provides good evidence that the levels of endotoxin are really driving incidence of diabetes. In these studies, researchers measure blood levels of endotoxin and then followed the subjects for 10 years. This is a big study, 6,000 people. And it turns out that the subjects with the highest levels of endotoxin at the beginning of the study, as seen with the black line here, these subjects ended up having much higher rates of diabetes.

Similarly, when they looked at the number of metabolic syndrome factors; high blood pressure, high triglycerides and so forth, it turns out that the higher the endotoxin level, the more the person suffered from metabolic syndrome 10 years later. Again, this is not proof, but is strongly suggestive that endotoxin is really very important.

As we mentioned before, it appears that endotoxin has these effects by stimulating the production of inflammatory cytokines. The term cytokine is a generic name for a diverse group of signaling molecules which modulate the functional activities of individual cells and tissues. Cytokines are

involved in all sorts of cell to cell communication processes, and in many respects, the biological activities of cytokines resemble those of traditional hormones. And it's also interesting to think of cytokines as either pro or anti-inflammatory. These two classes can either inhibit the other class or promote its own class.

Many cytokines show both stimulating and inhibitory activities with different concentrations or different situations, and so many synergize or antagonize the actions of other factors. It's really very complicated, but fascinating. But also important to know is that cytokines are critical for brain function, including normal learning and memory.

All of us know what it feels like when we feel sick. They're common features of many illnesses that cause to have a lack of appetite, body aches, fever, depressed mood. And cytokines cause these symptoms. That's why we feel down, we get the flu or even after we get vaccinated. When there is an abundance of these inflammatory cytokines, this is called a sickness syndrome. These are all cytokines effects. We all experience these many times. And what's really kind of fascinating is that we've just started to realize is that there are many commonalities with the cytokine effects and depression. Symptoms of depression are correlated with cytokine levels. And immuno-therapy, such as interferon, which is used to treat hepatitis C, can actually induce depression in a large number of patients. And conversely, cytokine blocker drugs like the ones that are used for treating psoriasis can actually reduce depression.

Cytokines induce the production of neurotransmitters such as serotonin which we all know is very important for depression as well. So there is a lot of evidence that diseases that are characterized by increased inflammation that this can lead to major depression. So there is growing evidence that depression can be thought of as a neuroinflammatory disorder in the brain, fascinating concept.

These inflammatory cytokines can affect the brain in numerous ways. As we mentioned before, they affect learning and memory. One of the most damaging things they can do is to trigger these white cells in the brain called microglia. These are macrophages in the brain. These microglia can promote normal neuro growth and repair and they are a key cell in the process of neuroinflammation. They become activated to the action of inflammatory triggers such as inflammatory cytokines but they can also be activated by other things in our environment like air pollution, heavy metals or even from the debris from damaged neuron.

What happens sometimes is that the effect of inflammation will induce these microglia to cause damage to the surrounding neurons. Once these neurons are damaged, the debris from those neurons can then stimulate more microglia. And this is sort of a cycle where you get ongoing damage and activation and inflammation in the brain. This process is thought to perhaps to be a part of a number of neurodegenerative diseases such as Alzheimer's disease and dementia. And this is one of the reasons why people with traumatic brain injury when they are 20 may develop dementia in their 30s and 40s.

This is a fascinating area of research and one which you will be no doubt hearing more about in the future. Because I studied alcoholism for so long, I'm really fascinated by this study here which shows in the state of alcoholics, the greater the permeability of the gut or leakiness, the greater the symptoms experienced by alcoholics. These symptoms, anxiety, depression, alcohol craving, obviously could promote alcoholics to keep drinking more alcohol. Of course, drinking more alcohol is ultimately going to cause more inflammation and make them feel worse, but in the short-term, it may make them feel better. I'm going to talk about that shortly here.

This slide really summarizes what could be going on. I really started to see that certain foods can alter gut microbiome and promote a leaky gut. And what happens in that case is that you get excess endotoxin leaking out of the gut going to inflame the adipose, the muscle in the liver causing insulin resistance and causing inflammation in the liver. Once the liver is inflamed, it creates even more inflammatory cytokines which can affect the brain and this is worse when there is a lot of alcohol on board.

Once the brain is induced to produce excessive cytokines, the microglia get involved, the neurons are killed, this can induce depression. Perhaps, one idea that I have been thinking about, is maybe this is one reason why people experience a loss of control or impulse control disorders where you get suicide or cravings for sweets and alcohol that you can't control. Of course once you start eating the wrong foods and drinking too much alcohol, then it goes back and affects the gut biome. And as a result of that process, the cycle continues in a really destructive way.

So how would we disrupt the cycle? Well, this is a fascinating study. You may have heard about fecal transplants. There is one study that shows that a fecal transplant from a healthy person can give normal insulin resistance to somebody who is otherwise insulin resistant. This is fascinating but as weird as it sounds since we know that the more types of bacteria that are present in the gut, the greater the diversity, the less overgrowth of gram-negative bacteria. This all sort of makes sense and we may be seeing more and more of this in the future. But for now, it's just a fascinating observation that you can use this fecal material to cure insulin resistance.

There are actually many bacteria that might be influencing a person's metabolism. Microbes may alter taste, change your appetite. It can also make you feel depressed or even make you feel good. Some of these factors are going to make us want to eat more. There is also a possibility that the bacteria will actually cause you to gain more calories from any particular kind of food. There is a recent study suggesting that the bacteria found in yogurt and other fermented foods can make us feel less energy. Pardon me, yogurt can make us feel less anxious, but if gut microbes are increasing the energy yield from food, this may one day be shown to influence weight gain.

There are actually a number of dietary factors that can influence the gut biome. These factors include the type of fat, the amount of fiber, type of fiber, the type of carbohydrate, degree of processing of food, as well as the amount of alcohol consumed. There are other factors that we know about which can influence the diversity of the gut biome. Antibiotics, even those given to your mother before you were born, may influence your gut biome and decrease the diversity. Breastfeeding can affect your biome in important ways and even being born vaginally may give you a different gut biome than if you were born by a Cesarean section. There is also the possibility of growing up in the very hygienic environment, may not give you as diverse and healthy a good biome as if you were exposed to lots of germs and bacteria when you were a child. All of these factors may be critically important because the gut biome influences gut permeability, systemic endotoxin and inflammatory cytokines.

This is an active area of research but it's clear that we need to rethink many traditional beliefs about what constitutes a healthy diet. The key may not be how the food that we eat affects us and our self but how the food that we eat affects the bacteria that live inside of us. This is a really fascinating way to think about diabetes, diets and I just look forward to learning more about this. I really can't give you any definitive advice yet because this is just cutting-edge research.

One day, we may recommend probiotics or prebiotics to treat some of the inflammatory diseases that we've been considering. Prebiotics such as the various types of food fiber we eat may have a bigger effect than we realize. Prebiotics promote the growth of good bacteria. Probiotics such as found in yogurt and other foods with live bacteria cultures may explain why yogurt is one of the healthiest foods we know about. It always seems to be associated with longevity.

Now that we learned a little bit, let's take a look at how this might relate to our population because we know that traditionally, Native Americans had almost none of these inflammatory diseases. First, let's consider stress. Stress can make the gut leaky through the action of the sympathetic nervous system. It can also dramatically influence inflammation.

In this diagram, I really wanted to show you how the brain could drive inflammation. As we noted before, cytokines from infection or injury or other sources of inflammation can signal the brain and make us feel depressed, or at least tell the brain there is extra inflammation going on. Conversely, the brain can also influence inflammation by making the gut more leaky during times of stress to the

sympathetic nervous system but also by acting through peripheral nerves to increase the release of inflammatory cytokines.

The brain can also reduce peripheral inflammation by stimulating the release of cortisol which will reduce inflammation as well as by directly acting through the autonomic nervous system. There is a sort of a reflex, which gives us feedback when the brain senses excessive inflammation so that the vagus nerve produces acetylcholine which then inhibits cytokine synthesis. This can be the source of many explanations for how we have psychosomatic effects and how our moods and how our social environment affects healing of all different kinds.

Now let's consider alcohol. Well, there is a tradition that alcohol has been used as a medicine. Here is an old prescription pad for the use of alcohol that was used during the prohibition. So there is really a conundrum. We think that drinking maybe a small bit of alcohol are maybe good for you, maybe anti-inflammatory, maybe reduce cardiovascular disease. But on the other hand, drinking a lot of alcohol every day can kill you and cause liver inflammation and neuroinflammation in the process.

Well, there is clearly a tipping point where too much alcohol is harmful. We know that excessive alcohol can alter the gut biome. Excessive alcohol will increase gut permeability and that will allow increased endotoxins to get into the portal circulation and it causes liver inflammation, liver injury, and increase inflammatory cytokines throughout the body.

Certainly, physical activity is much greater in traditional Native American societies than it is today. We know that physical fitness is one of the most powerful ways to reduce inflammation. This slide really illustrates that dramatically. It illustrates that exercise dramatically reduces the inflammatory response when these subjects were administered endotoxin. Exercise is one of the most powerful influences we know to reduce inflammation.

We have all heard a lot about vitamin D but it's crucial to remember that the normal source of 90% of our vitamin D is from sunlight. So that when we measure vitamin D, we are essentially measuring sunlight exposure. Sunlight has immune effects that are independent of immune effects of vitamin D, so sunlight maybe the reason why we see the benefits but nonetheless, there are benefits to getting vitamin D in oral form through foods.

In many cases, there is lots of data that shows that having a low vitamin D level is unhealthy. In this meta-analysis we see a combination of a number of studies which concludes that the baseline blood vitamin D levels will go on to predict the incidence of type 2 diabetes years later. Vitamin D has also been linked to a number of common inflammatory disorders.

Well, when I was in NIH studying suicide and I was really fascinated that the season of the year that when vitamin D levels were low, corresponded to the time of year when the rates of suicide were the highest. This made me wonder if suicide might be related to vitamin D levels and I found there are a number of reasons why this makes sense. Depression is associated with vitamin D gene variants for one. Two, low vitamin D was associated with reduced cognitive performance, psychotic symptoms, as well as the development of depression. And three, dietary vitamin D correlate with depression in some studies.

So to investigate this, I obtained samples from active duty service members in the military whose blood serum was available in frozen specimens saved by the Defense Medical Surveillance System. All these suicides were officially verified from service members and they were matched to control subjects who were randomly selected from the same population. And you could see from this graph that associates with the lowest level of vitamin D had more than twice the number of suicides of service members with healthy levels of vitamin D. But data also showed that more than 30% of service members are deficient in vitamin D, which sort of makes sense because in the military, you have to cover up and they do a lot of military operations at night. But with that, just last year, another study was able to replicate these findings showing an association of low vitamin D and suicide

but also implicated inflammatory cytokines. This sort of fits with the idea that vitamin D is working through an inflammatory mechanism.

So in this next study, we look at Indian country. In this study, we see that children with low levels of vitamin D on the left have a higher suicide risk and they also have higher levels of CRP which is an inflammatory marker. So in these children, we can see that this low vitamin D is really causing or is associated with more inflammation. Now we know we can fortify milk with vitamin D but obviously, these children are not getting enough from their milk. Well, actually, some would have to drink gallons of milk to get the same amount of vitamin D that they can get from less than half an hour of sunlight exposure.

So, we kind of need to be careful about our advice to avoid sun exposure. Certainly, that may reduce some kinds of skin cancer but we really don't know whether it'll reduce death from other causes, such as suicide. No one really knows the answer to these questions right now.

The last thing I want to talk about are the traditional sources of dietary fat and carbohydrates that may be really protective to Native Americans because they reduce inflammation to the endotoxin produced in the gut. I mean this is really intuitive. We know that traditional American dietary components like the "Three Sisters", seems like they are healthy food and in fact, this does promote a more healthy and diverse gut biome.

Here's one study which really hammers this home. This was a group of subjects who were given a prudent diet, which is essentially a high-fiber diet and it shows that after the prudent diet, the level of endotoxin in your blood was lowered very significantly.

This is another slide that kind of shows the importance of diet. One of the common components of modern diet which many people are concerned about is that we are now increasing our consumption of corn sweetener, high fructose corn syrup or fructose in the diet. This is the high fructose corn syrup that seems like it's in everything these days, from ketchup, to bread, to soft drinks. I think we all know that fructose is metabolized very differently from other sugars and in excess, it may have some toxic effects on the liver. It certainly has a very different effect on the gut biome.

Now in this study, we can see that the people who were given fructose drinks versus glucose drinks have a very different type of endotoxin. In other words, subjects who were given fructose drinks to drink, had increased levels of endotoxin, whereas if they're given just plain glucose drinks, the endotoxin didn't increase. This is kind of a crazy thing to advise people but if somebody can't give up their soft drinks, it's almost better to tell them to drink the Coca-Cola they get from Mexico, which is not sweetened with high fructose corn syrup because it may be less damaging to their livers and maybe less problematic. We really don't know yet but it's a fascinating thing to consider.

Other studies have found a link with high fructose corn syrup and a number of other diseases, obesity, depression, of course diabetes, non-alcoholic fatty liver disease, as well as aggression, and suicidal behavior in high school students. This all makes sense if you understand how this endotoxin could be affecting the whole body, including the brain. Again, none of this has been proven, these are just association studies. But you should be aware that there's a growing body of evidence, this high fructose corn syrup is really bad for us.

This slide shows some little rats that were given fructose or normal rat gel, both of these animals had the same exposure to calories but the high fructose corn syrup had a dramatic increase on the development of adiposity. This is really indicative that we need to be very careful about the use of this high fructose corn syrup.

I should also note that coffee turned to be anti-inflammatory. So that's another drink that we could recommend to people and in fact, that's the kind thing that can be done. This is just one case study. This is a 15-year old boy from our hospital here in Whiteriver, Arizona that was encouraged to stop drinking sodas, to just make one intervention in his obesity and you could see how he's way off the

chart in terms of his weight. Well, once he stopped drinking soda, his weight stabilized and after a few months, he joined a basketball team and as you can see, his weight joined the normal -- his normal peers. This is the kind of thing that we can really hope for, by basically a simple intervention, just encouraging people to stop drinking soft drinks.

I should mention here, there's some early data that suggests that perhaps the artificial sweetened soft drinks may affect the microbiome and that may cause detrimental effects. We just don't know for sure the answer to all these things.

Fat is very important also. Native American diet rich in fat and wild game will increase omega-3 fat, reduce inflammation, probably improve brain function and improve mood. Let's talk about this next.

The next slide please, looking at the graph. This is a graph of people who ate bison for six weeks. This picture shows that men who were either given regular beef from the grocery store or bison to eat every day, for six weeks, had a reduction in the inflammatory markers, particularly, the IL-6 and the C-reactive protein, which are markers of inflammation. So it turns out that liver inflammation and the amount of circulating endotoxin and alcoholism is influenced by the type of dietary fat that you eat.

Well, it turns out that omega-6 polyunsaturated fat, which is really the fat that's common in most of the foods that we feed laboratory animals or people promotes inflammation. However, if a diet is rich in saturated fat, for example, the fat that's in butter or natural lard or coconut oil, the gut will be much less prone to leak endotoxin and be much less prone to be inflamed than with a diet with omega-6 fatty acids.

Now, let's consider the polyunsaturated fats which include the omega-6 and omega-3 fatty acids. Like vitamins, these omega-3s and omega-6s are essential. Our body can't make them. We have to eat them in our diet. Omega-3 and omega-6 fats are similar, long, flexible molecules but they cannot be interconverted even though they're very similar. They're made into many of the same products in the body.

The American diet is abundant in omega-6 fat, which is present in oil from corn, peanuts, soy as well as in the poultry, beef, and pork that are in commodities. Even fish that's been tanked from soybeans is going to be high in omega-6 fat. In contrast, dietary omega-3 is often limited to seafood, of course it's in mother's milk, but it's in the green leafy plants and walnuts. What's important to understand is that this fat gets into our bodies and stays there for years.

One of my projects at NIH was to measure the brain uptake of the longest omega-3 fatty acid in our brain called "DHA". This is commonly found in fish. We found out that it had a half life of about two and a half years. This means that it takes about 10 years after you change your diet for it to take full effect. This is critical to understand because the effects of a diet deficient in omega-3 fat will last for a decade or more before the effects of an adequate diet are fully manifest.

Well, not only do Americans eat too little omega-3 fat but they also eat way too much omega-6 fat. Omega-6 fat is a source of inflammatory mediators, such as prostaglandins that are a critical factor in many inflammatory processes. Modern American diet is particularly abundant in the omega-6 fat that's from corn, peanuts, and soy. In this graph, you can see that there's been a dramatic increase in the production of soy oil, which is a very rich omega-6 source. You can see the consumption of soy oil in the United States has increased 1,000 fold in the last century. So now, on average, people consume almost 25 pounds per person per year. Soy can account for 83% of all the fat that we eat and it's highly concentrated omega-6 fat.

Well, there's other sources of omega-6 fats too, linoleic acid which is an 18 carbon omega-6 fat present in the soy oil is also in corn, peanut and safflower oil, and it has many pro-inflammatory metabolites. While we consume more omega-6, we eat fewer foods that are high in omega-3, as a

result, our diet contains perhaps 10 times as much omega-6 as omega-3. Whereas a century ago, we would've probably been getting equal amounts of both kinds of fatty acids.

Omega-3 fatty acids have many important health effects. Omega-3 fat can reduce inflammation and cytokines. Omega-3 fat is critical for brain function in the formation of neurons. Multiple studies suggest that omega-3 fat can improve mood, reduce cardiovascular disease, stroke and also treat arthritis. People have been using cod liver oils for treating arthritis for several centuries. I think the Greeks even describe using fish oil.

So here is a study that really demonstrates the importance of eating fish. So this is a study called the ALSPAC study that was conducted by Dr. Joe Hibbeln at NIH. He took a look at a big epidemiological study, the ALLSPACH study. This is a longitudinal study that looked at 14,000 mothers and 14,000 children and if you group the mothers on the basis of the amount of fish they consumed during pregnancy, you can see that the mothers who ate no fish to the left had much more depression than the mothers who ate fish frequently on the right.

What's really striking is when you look at the effect on the children that were born from these mothers. These children are seven years old and you can see that there is much fewer conduct problems in the children whose mothers ate lots of fish. The black lines represent girls and the red lines represent boys. You can see that the children of mothers who ate more fish over on the right, had much fewer behavioral problems than the children whose mothers ate no fish, over to the left. These behavioral problems are things like being obedient or lying, cheating or stealing, or having temper tantrums. These are really interesting studies. They don't prove the connection but these are studies that looked at many, many variables, socioeconomic study variables, 23 different variables went in to the statistics to look at this. Socioeconomic status and other factors were all considered in these studies, to really give us a very strong indication that eating fish during pregnancy might not be so bad as they say.

There's a lot of controversy over the mercury in fish but, most recent studies have confirmed what those of us in the field know, is that the benefits of eating fish seem to outweigh whatever slight neurological risk of mercury there is. Particularly fish has not only mercury, it has omega-3, it has selenium and it may be that selenium helps protect against mercury when you actually consume it in the fish. There are lots of studies coming out about this and I want you to be aware that I'm not making any recommendations, but I'm showing you what the data says. I think that the future will hold, perhaps different dietary recommendations about eating fish during pregnancy.

So the effect of omega-3 is perhaps most definitively seen in this slide here. This is a study that was done at Harvard by Dr. Andrew Stoll a number of years ago. He was treating people with arthritis and he noted that fish oil would reduce not only the pain of arthritis but it could also reduce depression. So he did a randomized placebo controlled double blind study, looking at severe bipolar depression. These are individuals who were so mentally ill that they required multiple hospitalizations for their illness and they went to the hospital multiple times.

In the survival analysis, you can see that the subjects on placebo were much more likely to relapse and require hospitalization than the subjects who were given fish oil. The trial stopped early because the oversight committee felt it was unethical not to provide fish oil to all the subjects. This is a high dose of fish oil. This is 6 grams of EPA and DHA, 14 capsules a day. This kind of study really makes you realize that some people might really benefit from this. I had a friend of mine who was involved with a Salvation Army program for addicts, and he used this. I'll show you. This is another slide that shows that more fish consumption in a particular country seems to be associated with less depression. What's really interesting about this slide is you could change the title and it would look the same, for whether you're looking at bipolar depression, whether you're looking at postpartum depression, whether you're looking at cardiovascular disease or stroke, seems like the countries that eat a lot of fish have much different diseases that they're suffering from.

This is the study that I wanted to -- this wasn't a study. This is just a friend of mine who decided he would try my idea out on some of the worst addicts in their program. As a result of this small experiment, they got a write-up in the Tucson paper because there was such a dramatic improvement in these men that were suffering from substance abuse. So I'm not going to read this whole thing but you can go back and look at the whole story. It's really fascinating. Again, it doesn't affect everybody but some people are really going to respond to the use of fish oil if they have psychiatric issues.

So what kinds of recommendations are there at the current date. The American Psychiatric Association recommends that patients with mood and impulse control disorders and so forth, should consume a thousand milligrams or a gram a day of a long omega-3 fatty acids, EPA and DHA. The American Heart Association recommends basically the same thing for people with cardiovascular disease, preferably from oily fish. I would suggest that eating the fish is probably better than eating the fish oil (it's also fascinating to realize that lowering omega-6 may have the same effect).

This is particularly important because the average American woman is only consuming a small fraction of the recommended amount of omega-3 for these disorders. A typical American might eat 70 milligrams a day instead of 1,000 milligrams a day of this fish oil. It's important to recognize the supplements that contain up to 3,000 milligrams are generally recognized as safe by the FDA. Doses much, much higher than this have been used in many studies.

Of course as I mentioned before, some groups are concerned about mercury levels in seafood like swordfish but there's no mercury in the fish oils. The side effects are generally -- the GI side effects belching or mild GI side effects and I'm not aware of any published reports of any actual harm resulting from -- or serious harm resulting from anybody taking fish oil. Theoretically, fish oil can reduce the clotting time but this hasn't really caused any serious problems that I'm aware of.

In the future, we may find that we can achieve the same effects that we get from increasing omega-3 fatty acids by reducing the amount of omega-6 fatty acids. In fact, the American Heart Association's recommendation to include corn oil and so forth as part of a healthy diet is really coming into a lot of question lately because there's been a recent reanalysis of studies that supported that by Dr. Chris Ramsden at the NIH who reanalyzed a lot of the original data and found that in fact, if you give omega-6 fat in say safflower oil, you don't really see any benefit and may actually see some harm.

You may be aware that there are algae-derived forms of DHA that can be microencapsulated and added to bread or other foods which maybe important if we want to avoid over fishing. Breast milk is high in DHA and that may be important also. Animal feeds can be supplemented with seaweed, flax seed or other sources of omega-3 fats and the resulting meat will turn out to have a higher levels of omega-3 fats. Eggs for example, are often marketed for their high DHA content. Range fed animals such as bison have higher omega-3 content in their tissues because they don't get fattened on corn and soy, and it maybe would be really much better for us than traditional beef and poultry that's fed corn and soybeans and feeds.

It may also be very important to recommend that our patients cook with low omega-6 oil, like canola oil or olive oil, which has more omega-3 and less omega-6. In the future, we may be able to find alternate varieties of soybeans that are genetically modified to be low in omega-6.

Here's some different fish to show that if you eat fish three times a day, say salmon three times a day, you're going to get plenty of omega-3s. Again, going back to this original diagram, I just want to review and say that diet, stress, inflammation and the gut biome can all influence the amount of endotoxin that gets from the gut into the circulation. Endotoxin, once it gets in the circulation can cause an inflammatory action throughout the body that affects everything and this is all signaled by the cytokines.

So in summary, I just wanted to emphasize that diseases found in modern western society tend to occur together and can be thought of as inflammatory symptoms. The risk factors associated with these diseases, all increase inflammation, and they're all related to excessive endotoxins in the circulation.

Through inflammatory mechanisms, endotoxins, from microbes in the gut, have been associated with all of these common inflammatory symptoms. Also, I think it's important to realize that the diet probably has two essential functions -- one, to provide nutrients for human cells, but also to provide a substrate for a healthy gut microbiome. The extent to which gut microbes influence appetite, metabolism, endocrine function and behavior is unknown, but it's likely to be very significant.

Clearly, many aspects of pre-modern or traditional American-Indian lifestyle could be reducing inflammation through these mechanisms, including getting outdoor exercise, where you're exposed to the sun and consuming traditional foods, traditional dietary fat and carbohydrates. In the future, an approach to diabetes treatment may recommend foods based on their pre-biotic effect as well as their caloric effect. One day, we may recommend that people replace fructose sweetened drinks with something like coffee which is thought to promote a healthy biome, maybe anti-inflammatory. And as I have also mentioned, we may benefit tremendously by reducing the omega-6 fat in our diet and increasing the omega-3 fat through consumption of different vegetable oils and the consumption of animals and fish, raised on such foods.